REMARKS

Claims 1-14 are pending. Claims 4-12 are withdrawn as drawn to a non-elected invention. Claim 2 is canceled herein. Claims 1, 3, 13 and 14 are amended herein. New claims 15-18 are added. Support for the amendments to claims 1, 3, 13 and 14, and for new claims 15-18, can be found throughout the instant specification as filed. Specific support for the amendment to claim 3 can be found at least at page 21, lines 1-8 of the instant specification as filed. Support for the amendments to claim 1 and for new claims 15-18 can be found at least in the sections at page 17, line 20 to page 26, line 30 and at page 96, line 12 to page 99, line 2 of the instant specification as filed. No new matter has been added by way of these amendments. The amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Priority

Applicant submits herewith a certified copy of the 0301566.6 application as required by 35 U.S.C. 119(b).

Withdrawn Objections/Rejections

Applicant acknowledges the Examiner's withdrawal of previous objections to the specification in view of embedded hyperlinks; and to claims 1-3 for alleged inclusion of non-elected subject matter.

Applicant additionally acknowledges the Examiner's withdrawal of the previous rejection of claims 1-3 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness, and of the previous rejection of claims 1-3 under 35 U.S.C. §102(b) as allegedly anticipated by Dewaste *et al.* (*Biochem J.* 2000; 352: 343-351).

Objection to the Specification

The Examiner has maintained an objection to the instant specification for reference to the proteins of Table 1B by GenBank number. The Examiner asserts that "[t]he specification does not refer to the date on which the GenBank sequences were accessed, so it is unclear whether the sequences were those that existed on the filing date or previous incarnations thereof." Applicant respectfully reminds the Examiner that, as set forth in MPEP 2163.02, compliance of a specification with the written description requirement under 35 U.S.C. §112, first paragraph, is assessed ***as of the filing date***. Consistent with such evaluation of the written description requirement, Applicant respectfully submits that the GenBank numbers presented in Table 1B must be assessed ***as of the filing date***. With respect, Applicant disagrees that the metes and bounds of the GenBank accession numbers presented in Table 1B are unclear because the sequences defined by these accession numbers were present in the GenBank database before the filing date of the current application. As was well understood by a person skilled in the art, the reference accession numbers utilized by GenBank may change as subtle changes in the details of the sequence identified by a given gene are found and agreed upon by members of the scientific community. As such, when changes are identified, the sequence associated with the GenBank accession number is revised, and the newly revised sequence listing is posted on publicly accessible databases such as the NCBI site. The history of these revisions is also documented at sites such as http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi. As such, the reference accession numbers listed in Table 1B of the instant specification each have a single and specific meaning as of the filing date of the instant application. The fact that a previous or post-filing date version of a selected sequence, as referred to by this reference accession number, existed before the filing date of the current application is not relevant, and does not render the use of the reference accession number indefinite. Rather, the reference accession number refers to only a single sequence as of the filing date of the current application. Accordingly, Applicant respectfully requests withdrawal of this objection.

Objection to Claim 3 Under 37 C.F.R. 1.75(c)

The Examiner has objected to claim 3 under 37 C.F.R. 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant respectfully submits that, without acquiescing to the validity of the Examiner's

objection and solely in the interest of expediting prosecution, Applicant has amended claim 1 to clarify that the signals presented therein include ***a signal generated from the interaction of the agent with ITPKC***. Applicant has also amended claim 3 to require that said signal generated from the interaction of the agent with ITPKC is a change in the phosphotransferase activity of inositol-1, 4 5-triphosphate 3-kinase C. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this objection.

Rejection of Claims 1-3 and 13-14 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-3 and 13-14 under 35 U.S.C. §112, first paragraph, because, according to the Examiner,

> the specification, while being enabling for (1) carrying out the claimed method in cells, wherein the method of identifying an agent that modulates the full length of the protein encoded by the gene for inositol 1,4,5-triphosphate 3-kinase C (ITPKC) or (2) a method of identifying an agent that modulates the function of full length protein ITPKC, comprising providing a preparation containing said ITPKC; incubating the preparation with a test agent to be screened under conditions to permit binding of the test agent to ITPKC; determining whether the test agent interacts with ITPKC by detecting the presence or absence of a an apoptotic signal, selected from the group consisting of: caspase activation, does not reasonably provide enablement for the methods as claimed.

Applicant respectfully traverses the foregoing rejection for the reasons set forth below. As amended, claims 1, 3, 13-14, and new claims 15-18, are directed to methods for identifying an agent that modulates the function of ITPKC that requires incubating an ITPKC preparation with a test agent under conditions to permit binding of the test agent to ITPKC, and determining whether the test agent interacts with ITPKC by detecting the presence or absence of a signal generated from the interaction of the agent with ITPKC. Applicant submits that, based on the teachings in Applicant's specification and the knowledge generally available in the art at the time of the invention, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation.

The Examiner has specifically asserted that

> the specification, while being enabling [for] a method of identifying an agent that modulates the full length of the protein encoded by the gene for ITPKC, does not reasonably provide enablement for a method of identifying an agent that modulates the protein fragment as shown in SEQ ID NO: 226. Applicants

> amended the claim to recite modulates the function of "ITPKC", however, the specification defines the apoptosis associated proteins broadly; for instance, see paragraph [0038]:
>
> In an additional aspect, the invention features a method of modulating apoptosis in a cell, where the method includes: (a) transforming into the cell a double stranded nucleic acid sequence encoding a polypeptide having at least 80% sequence identity with a polypeptide having a sequence as set out in Table 1B . . . and (b) culturing the cell . . . for this reason, the claims, including new claims 13-14, still encompass fragments of ITPKC that may be non-functional in the claimed methods, and the issues raised in the original rejection are still applicable here.

Applicants respectfully submit that the instant claims recite a method for identifying an agent that modulates ITPKC; the claims recite "ITPKC," not an "apoptosis associated protein" as asserted by the Examiner. In addition, the passage of the instant specification cited by the Examiner is irrelevant with respect to the instant claims. The claims are directed to methods for identifying an agent that modulates the function of ITPKC and are not broadly drawn to "a method of modulating apoptosis in a cell," as described in the above-cited passage. The polypeptide sequence of ITPKC was known in the art at the time of filing (indeed, the Dewaste *et al.* prior art reference relied upon by the Examiner discloses GenBank accession number AJ290975 to identify the ITPKC polypeptide sequence). Thus, one of ordinary skill in the art at the time of filing could recognize the scope of the instant invention to encompass methods for identifying an agent that modulates the function of an ITPKC polypeptide, wherein the term "ITPKC polypeptide" was known to have a specific sequence as disclosed in the art surrounding such ITPKC polypeptides. Accordingly, the skilled artisan would be able to make and use the claimed invention in a manner consistent with the scope of the claims as presently amended.

> The Examiner has additionally asserted that
>
> [r]egarding claims 1-3, apoptosis is programmed cell death (see definition at p. 489, left column, 1st paragraph and Figure 1 of Saikumar et al. Am J. Med. 1999; 107:489-506). As is clear from Figure 1 of Saikumar et al., cell death requires the presence of a cell. Amended claim 1 recites "[a] method of identifying an agent that modulates the function of inositol-1,4 5-triphosphate 3-kinase C (ITPKC), comprising providing ***a preparation*** containing said ITPKC; incubating ***the preparation*** with a test agent to be screened under conditions to permit binding of the test agent to ITPKC; determining whether the test agent interacts with ITPKC by detecting the presence or absence of a ***an apoptotic signal, selected from the group consisting of: caspase activation, DNA fragmentation, cell death, lack of cell proliferation, amount of G1 DNA, change in mitochondrial membrane potential, or externalization of phosphatidylserine***, and the signal generated from

> the interaction of the agent with ITPKC, and thereby determining whether the test agent modulates the function of ITPKC. The measurement of apoptotic signals recited in claim 1 (cell death, lack of cell proliferation, amount of G1 DNA, change in mitochondrial membrane potential and externalization of phosphatidylserine require presence of a cell. A "preparation" encompasses a cell free system or some other type of non-cellular assay.

In contrast to the Examiner's assertions, the scope of the claims as amended is commensurate with the disclosure in Applicant's specification.

Solely in the interest of expediting prosecution of the instant invention, claims 1, 3, 13 and 14 have been amended to require performance of a method for identifying an agent that modulates the function of ITPKC *via* incubation of a cell expressing ITPKC with a test agent. The Examiner acknowledges that the specification is enabling for such a cell-based assay. Indeed, the instant specification fully enables such cell-based assays for identifying an agent that modulates the function of ITPKC involving detection of determining whether the test agent interacts with ITPKC by detecting the presence or absence of a signal selected from the group consisting of caspase activation, DNA fragmentation, cell death, lack of cell proliferation, amount of G1 DNA, change in mitochondrial membrane potential, externalization of phosphatidylserine, or a signal generated from the interaction of the agent with ITPKC.

Applicants further submit that new claims 15-18 are enabled by the teachings of the instant specification in view of the knowledge of one of ordinary skill in the art at the time of filing. Claims 15-18 encompass performance of not only cell-based assays but also assays that do not require the presence of a cell, and specifically require detection of a caspase activation signal or a signal generated from the interaction of the test agent with ITPKC. It is well settled that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). As stated in *Forman*, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

Enabling support for performance of assays as recited in claims 15-18, that do not require the presence of a cell, can be found in the instant specification as filed. Specifically, Applicants refer the Examiner to the section at page 95, line 17 to page 96, line 11 of the specification as filed, where Applicants have disclosed that "[s]ubstances which inhibit or affect kinase activity may be identified by means of a kinase assay as known in the art, for example, by measuring incorporation of ^{32}P into a suitable peptide or other substrate in the presence of the candidate substance." Such *in vitro* assays were well known in the art at the time of filing and the skilled artisan would recognize that such assays could be readily applied to detecting ITPKC activity. For example, prior to the filing date of the instant application, Communi *et al.* (*J. Biol. Chem.* 1999 274:14734-14742, a copy of which is submitted herewith as Appendix A) described detection of ITPK kinase activity *via in vitro* measurement of ^{32}P incorporation into a substrate. It is also notable that the very prior art reference relied upon by the Examiner (Dewaste *et al.*) teaches an *in vitro* IP3 kinase activity assay (refer, for example, to page 345, right column, "HPLC analysis").

Applicants further note that the Examiner has acknowledged the availability of cell-free systems in the prior art for studying caspase activation; however, the Examiner has concluded that although caspase activation was studied in cell free systems, the claims require the study of the interaction between ITPKC and a test agent, and neither the specification nor the literature teach a cell-free system in which a test agent is screened to permit binding of the test agent to ITPKC and measuring apoptosis." Applicants again submit that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation," not whether the prior art provides step-by-step directions for performance of the instant invention as claimed. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). Indeed, it is the fact that the prior art does ***not*** teach each step of the claims that renders the invention novel. As detailed above, the instant specification describes performance of assays that do not require the presence of a cell in a manner sufficient to enable the skilled artisan to practice the claimed methods using no more than routine experimentation. Applicants respectfully submit that nothing more is required. Accordingly, in view of the teachings of the instant specification and the extensive knowledge in the art at the time of filing regarding *in vitro* assays for detection of signals such as those disclosed in the instant specification, Applicants respectfully request

reconsideration of the Examiner's assertion that Applicants have only enabled performance of the methods of the instant claims in a cellular system.

Finally, the Examiner has asserted that the subcellular localization of ITPKC might require performance of cell-based assays. Applicant submits that the invention must be given the presumption of correctness and operativeness. As set forth in *In re Marzocchi*, 439 F.2d 220,

> [a]s a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112.

Whereas the Examiner has asserted that subcellular localization ***might*** be an important determinant of the apoptotic signaling activity of ITPKC activity, such conjectural assertions regarding ITPKC activity are insufficient to overcome the above-stated presumption of operativeness. As disclosed in the instant specification, Applicants have discovered a robust association between ITPKC levels and apoptotic activity and have presently claimed embodiments that are commensurate in scope with the teachings of the instant specification. Thus, in view of all of the foregoing, Applicant submits that based on the teachings and guidelines of the present invention as disclosed in the application, in combination with the knowledge of one of skill in the art at the time the application was filed, the methods for identifying an agent that modulates the function of ITPKC *via* incubation of an ITPKC preparation with a test agent under conditions to permit binding of the test agent to ITPKC, and determining whether the test agent interacts with ITPKC by detecting a signal generated from the interaction of the agent with ITPKC are routine to one skilled in the art. Indeed, in view of the ample guidance provided in the specification and the references cited therein, and the extensive knowledge available in the art, the instant specification enables a person of ordinary skill in the art to make and use the claimed methods without undue experimentation. Accordingly, Applicant respectfully requests that the foregoing rejection of claims 1-3 and 13-14 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejection of Claims 13-14 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 13-14 under 35 U.S.C. §102(b) as being anticipated by Dewaste *et al.* (*Biochem J.* 2000; 352:343-351). Applicant respectfully traverses this rejection. As the Examiner is aware, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Claim 13 and dependent claim 14 as amended are directed to a method for identifying an agent that modulates the function of ITPKC that requires incubating an ITPKC preparation with a test agent ***under conditions to permit binding of the test agent to ITPKC, wherein the test agent is a low molecular weight organic molecule***, an antibody or antibody fragment, an antisense oligonucleotide, a small inhibitory dsRNA, or a ribozyme, and determining whether the test agent interacts with ITPKC by detecting the presence or absence of ***a signal generated from the interaction of the agent with ITPKC***. Dewaste *et al.* does not teach or suggest performance of a method for identifying an agent that modulates the function of ITPKC, wherein the test agent is ***a low molecular weight organic molecule***, antibody or antibody fragment, antisense oligonucleotide, small inhibitory dsRNA, or a ribozyme, and detecting the presence or absence of ***a signal generated from the interaction of the agent with ITPKC***, as required by the instant claims. Rather, Dewaste *et al.* teaches that under certain conditions, mammalian ITPKC may be purified using calmodulin-sepharose affinity chromatography (refer to page 347, second column of Dewaste *et al.*) and that calmodulin may be used to sequester calcium, thereby modulating calcium levels, which, in turn, may modulate levels of ITPKC kinase activity. Contrary to the Examiner's assertion, calmodulin does not fall within the definition of "low molecular weight organic molecule" set forth in the instant specification. The instant specification defines a "low molecular weight organic molecule" to possess a size "less than about 5000 Daltons" (refer, *e.g.*, to page 25, lines 19 and 20, of the instant specification as filed). Calmodulin is a protein of approximately 17000 Daltons in size (refer, *e.g.*, to Sacks *et al.* (1992) *Biochem J.* 286:211-216 and Wallace and Cheung (1979) *J. Biol. Chem.* 254:6564-6571, attached herewith as Appendices B and C, respectively) – a size that is significantly larger than that defined in the instant specification as "a low molecular weight organic molecule." In addition, Applicant respectfully submits that calmodulin ***does not interact with ITPKC to generate a signal***, as is required by the instant claims. Rather, calmodulin modulates calcium levels *via* sequestration, which in turn can

modulate ITPKC kinase activity levels. Accordingly, Dewaste *et al.* fails to teach or suggest incubating an ITPKC preparation with a test agent that is ***a low molecular weight organic molecule***, antibody or antibody fragment, antisense oligonucleotide, small inhibitory dsRNA, or a ribozyme, under conditions ***to permit binding of the test agent to ITPKC***, and determining whether the test agent interacts with ITPKC ***by detecting the presence or absence of a signal generated from the interaction of the agent with ITPKC***. Thus, Applicant submits that Dewaste *et al.* does not anticipate the claimed invention. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 13-14 under 35 U.S.C. § 102(b).

SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance. If a telephone conversation with Applicant's undersigned representative would move this application to allowance faster, the Examiner is urged to call (617) 439-4444.

Dated: August 10, 2007

Respectfully submitted,

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